ATTORNEY DOCKET NO. 14014.0346U1
PATENT

REMARKS

Claims 1-52 are pending in this application. Applicants gratefully acknowledge the rejoinder of Groups I-IV. Claims 39-52 are withdrawn from consideration, as drawn to non-elected inventions of Groups V-VIII. Claims 11, 22, 24 and 28 are canceled herein without prejudice. Claims 1, 4, 12, 15, 23, 27, 31-34 and 36 are amended herein to more particularly define the invention. Support for these amendments can be found in the original claim language and throughout the specification, as set forth below. Further, submitted herewith is a Petition under 37 C.F.R. §§ 1.78(a)(3) and 1.17(t) to Accept an Unintentionally Delayed Claim for Priority under 35 U.S.C. § 119(e). It is believed that these amendments and Petition add no new matter. In light of these amendments, Petition and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims.

35 U.S.C. § 101

Claims 1, 3-12 and 14-22 are rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory matter. Specifically, the Office Action states that claims 1, 3-12 and 14-22 do not sufficiently distinguish over cells as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products.

Claims 11 and 22 are canceled herein without prejudice, thereby rendering moot this rejection as it applies to these claims. Claims 1 and 12 are amended herein, according to the

Examiner's suggestion, by the insertion of the term "isolated." Applicants believe that this rejection is overcome and respectfully request that it be withdrawn and that amended claims 1 and 12 and dependent claims 3-10 and 14-21 be allowed.

35 U.S.C. § 112, second paragraph

A. Claims 1-38 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action states that the term "substantially homologous" in claims 1, 12, 23, 27, 32, 33, 34 and 36 is a relative term, rendering the claims indefinite.

"Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." M.P.E.P. § 2173.05(b). In *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988), "the court held that the limitation 'which produces substantially equal E and H plane illumination patterns' was definite because a person of ordinary skill in the art would know what is meant by "'substantially equal.'"

Applicants believe that a person of skill in the art, in light of the specification, would understand what is meant by the term "substantially homologous." Specifically, a person of skill in the art of polypeptides would know that an amino acid sequence that is substantially homologous to a reference amino acid sequence would include one or more additional amino acids, one or more deletions of amino acids or one or more substitutions in the amino acid

sequence without appreciable loss of functional activity of the reference amino acid sequence. See in the specification page 15, line 31 to page 16, line 4. Thus, a growth factor that is substantially homologous to GLP-1 and/or exendin-4 would include one or more additional amino acids, one or more deletions, or one or more substitutions in the amino acid sequence of GLP-1 and/or exendin-4 respectively, without appreciable loss of functional activity of GLP-1 and/or exendin-4 in regard to the ability to differentiate insulin-producing cells from non-insulin-producing cells. Therefore, applicants believe that these rejections lack merit and respectfully request that these rejections be withdrawn and that claims 1, 12, 23, 27, 32, 33, 34 and 36 be allowed.

B. Claims 4 and 15 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for the recitation of "non-islet cells." Specifically, the Office Action states that by definition, "islet cells" are a cluster of cells, which allegedly does not specify a type of cells, and is not limited to islets of Langerhans.

Claims 4 and 15 are amended herein by deleting "non-islet cells" and substituting therefor "cells that are not pancreatic beta cells." See in the specification page 14, lines 4-10. Applicants believe that this amendment overcomes the rejection based on indefiniteness and respectfully request withdrawal of this rejection and allowance of amended claims 4 and 15.

C. Claim 37 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for the recitation of "by bolus at least once." Specifically, the Office Action states that

"bolus" is used in the art to mean a single, large dose; therefore, it allegedly is not clear what the metes and bounds of "bolus" are, if it can be a repetitive dose.

The term bolus is not indefinite because a person of skill in the art of administering medications would understand that "by bolus" means that the substance being administered to a subject is given all at once. Moreover, the term "bolus" does not require that the dose of the medication be large. For example, a physician can administer a small dosage of medication into a vein of a subject through a needle or catheter over a prolonged period of time, i.e., several minutes to hours, with a slow "intravenous drip." Alternatively, a physician can administer the same dosage of medication into a vein of a subject through a needle or catheter all at once by quickly advancing the plunger of a syringe in an "intravenous push." One of skill in the art would recognize that the intravenous push is a bolus.

Moreover, a dosage of medication can be given by bolus on more than one occasion. In fact, in U.S. Patent No. 5,424,286 (the '286 patent) cited by the Office, in the "Brief Description of the Drawings" section, Figure 3 is described as "a graph illustrating the effect of exendin with and without antagonist.... Exendin-4 (1 nmol) was given as an intravenous bolus at 60, 120 and 180 min...." See column 3, lines 45-51. A skilled artisan would recognize that a dosage of 1 nmol is not large and was administered as a bolus three times. Thus, the metes and bounds of "by bolus at least once" are known to a person of skill. Therefore, applicants respectfully believe that this rejection is without merit and respectfully request that it be withdrawn and that claim 37 be allowed.

35 U.S.C. § 112, first paragraph

Claims 32 and 33 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office Action states that claims 32 and 33 are directed to a method of promoting pancreatic amylase producing cells to produce amylase using GLP-1 or exendin-4. The Office Action goes on to state that a person of skill allegedly would not know how to use the present invention to promote pancreatic amylase producing cells to produce amylase using GLP-1 or exendin-4 as claimed because the experiment results in the instant application and the prior art indicate that neither GLP-1 nor exendin-4 can stimulate amylase release.

Applicants respectfully point out, however, that the claim is directed to producing insulin production in a cell that already produces amylase, without the loos of amylase function. For clarification and in a effort to facilitate prosecution of this application, claims 32 and 33 are amended herein by deleting the words "both" and "and amylase." Deleting these words from the claims removes the basis for the enablement rejection. Therefore, applicants respectfully request that this rejection be withdrawn and that amended claims 32 and 33 be allowed.

35 U.S.C. § 102

A. Claims 1, 3-10, 12, 14-21, 23, 26, 27, 30, 31 and 36-38 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Eng, U.S. Patent No. 5,424,286 (the '286 patent). The Office Action states that the '286 patent teaches that GLP-1 and exendin-4 are useful

insulinotropic agents and can be used in the treatment of diabetes mellitus and that exendin-4 can be used for the treatment of Type 1 and Type 2 diabetes. The Office Action states that the '286 patent does not state explicitly the effect of GLP-1 or exendin-4 on converting non-insulin-producing cells into insulin-producing cells. Nevertheless, the Office alleges that a converted population of cells inherently exists in the treated animals as the prior art consists of the same steps described in the present claims.

For a prior art reference to anticipate a claimed invention, each and every element of the claimed invention must be disclosed in that single reference. Further, the disclosure in that single reference must be enabling. If one element of the claimed invention is not disclosed in the prior art reference, there is no anticipation. It is settled law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently." *Verdegaal v. Union Oil*, 814 F2d. 628, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987).

Claims 1, 12, 23, 27 and 31 are amended herein by adding the phrase, "for at least twenty-four hours." Further, claim 36 is amended to recite "[a] method of inducing insulin secretion in a subject, comprising administering to the subject a growth factor selected from the group consisting of Exendin-4, growth factors having amino acid sequences substantially homologous to Exendin-4, and fragments thereof, wherein the Exendin-4 contacts non-insulin-producing cells for at least twenty-four hours, and wherein the non-insulin-producing cells are differentiated into insulin-producing cells." The '286 patent does not expressly disclose each and every element of these amended claims. Specifically, the '286 patent does not teach that the growth factor contacts non-insulin-producing cells for at least twenty-four hours. Furthermore, the

patent does not teach that non-insulin-producing cells are differentiated into insulin-producing cells by contact with a growth factor for at least twenty-four hours. Applicants believe that these amendments overcome this rejection and respectfully request that this rejection be withdrawn and that amended claims 1, 12, 23, 27, 31 and 36 and dependent claims 3-10, 14-21, 26, 30 and 37-38 be allowed.

Regarding inherency, M.P.E.P. § 2112 requires the Examiner to provide a rationale or evidence tending to show inherency. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App.& Inter. 1990) (Emphasis in original). Thus, for a claim to be rejected on the basis of inherency, the Examiner has the burden to show that a missing element of a claim is inherently present in the prior art and that this missing descriptive matter would be recognized by persons of skill in the art.

Applicants respectfully assert that the prior art does not inherently anticipate the claimed invention. The following describes the legal foundation for this conclusion.

In *In re Zierden*, 162 USPQ 102 (CCPA 1969), the question presented was whether claims to a method of removing alluvium from industrial waters, for example, water in cooling systems, were anticipated by a prior art reference [French patent] that disclosed a method for treating industrial waters to remove calcium carbonate scale that builds up in such cooling systems. The court held that because the prior art reference did not inherently teach that the

industrial waters contained alluvium, the disclosed method did not necessarily result in the removal of alluvium. Thus, there was no anticipation of the claimed invention.

The dissenting judge stated that "if the industrial waters of the [prior art] French patent contain alluvium, even in a very slight amount, then the process of that patent inherently anticipates appellant's process as claimed here." (Emphasis added) There was no dispute between the majority and the dissent that if allvium had been present in the waters, the prior art process would have inherently removed the alluvium. (Emphasis added). Further, it was not disputed that it was very likely that alluvium was present in the waters. The majority opinion was based on the lack of certainty that alluvium was present in the waters.

In *Hansgirg v. Kemmer*, 102 F.2d 212, 40 USPQ 665 (CCPA 1939), the court emphasized that for a prior art reference to anticipate a claimed invention, the matter not explicitly described in the reference must necessarily be present in the reference. The court held that "[i]nherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

The law on probabilistic inherency is set forth in *Continental Can v. Monsanto*, 948 F.2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991). The court held that "[t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." (Emphasis added).

With regard to the Office Action's rejection of claims 1, 3-10, 12, 14-21, 23, 26, 27, 30, 31 and 36-38 on the basis of inherency, the Office has the burden to show that the '286 patent inherently describes an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof.

The '286 patent teaches pharmaceutical compositions containing exendin-4, fragments thereof, and methods for the treatment of diabetes mellitus. The patent further teaches "a method for the enhancement of insulin production or expression which comprises the steps of providing to a mammalian beta type pancreatic islet cell an effective amount of the insulinotropic peptides" disclosed. The patent does not mention differentiating non-insulin-producing cells into insulin-producing cells and does not teach contact for twenty-four hours. In *Hansgirg*, the issue was whether a prior art reference anticipated a method claim for obtaining purified magnesium. The court found that the prior art reference did not anticipate the claimed invention, noting "[n]othing is disclosed in his application that he sought to separate dust from vapor or that it was any part of the problem he was attempting to solve." Similarly, nothing is disclosed in the '286 patent to demonstrate that differentiating non-insulin-producing cells into insulin-producing cells was part of the problem to be solved.

Further, the Office is incorrect if it assumes that methods of stimulating insulin release in a mammal as taught in the '286 patent necessarily differentiates non-insulin-producing cells into insulin-producing cells. The patent teaches contacting beta cells with exendin-4 for one hour (Example 4), and administering repeated boluses of exendin-4, as shown in Figure 3. In contrast, the instant application teaches an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof. Applicants disclose that it took at least twenty-four hours for non-insulin-producing cells to differentiate into insulin-producing cells. See in the specification Example 3, page 41, lines 19-22. Thus, in the method of the '286 patent, in which contact between non-insulin-producing cells and exendin-4 lasted for only a few hours, a person of skill would not expect to find differentiation of those cells into insulin-producing cells. Thus, the Office has failed to meet its burden of showing that the missing matter in this reference, an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof, is necessarily present. *Hansgirg*, 102 F.2d 212.

It is error for the Office to reject claims 1, 3-10, 12, 14-21, 23, 26, 27, 30, 31 and 36-38 because it is possible or even probable that some of the insulin-producing cells claimed in the instant application may have been present in the '286 patent. The Examiner has failed to show

with certainty that the missing matter (the cells) is present, and, thus, there can be no anticipation of these claims based on inherency. Therefore, applicants respectfully request that this rejection be withdrawn and that amended claims 1, 12, 23, 27, 31 and 36 and dependent claims 3-10, 14-21, 26, 30, and 37-38 be allowed.

B. Claims 2, 13, 25 and 29 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Raufman *et al.* (*J. Biol. Chem.*, 1992, 267(30):21432-37). The Office Action states that Raufman *et al.* discloses that GLP-1 analogue, GLP-1(7-36), interacts with exendin receptors on dispersed acini from guinea pig pancreas. Specifically, the Office Action states that the reference teaches that dispersed acini from guinea pig pancreas were treated *in vitro* with either GLP-1 or exendin-4 and the effect of the compounds on amylase release from the treated acini was analyzed. The Office Action states that the reference is silent regarding the effect of GLP-1 or exendin-4 on converting non-insulin-producing cells of acini into producing insulin-producing cells. Nevertheless, the Office alleges that a converted population of cells inherently exists in the treated acini because this prior art reference consists of the same steps described in the present claims.

Claims 2, 13, 25 and 29 depend from amended claims 1, 12, 23 and 27 that now recite "for at least twenty-four hours." Raufman *et al.* does not expressly disclose each and every element of claims 2, 13, 25 and 29. Specifically, the reference does not teach that the growth factor contacts non-insulin-producing cells for at least twenty-four hours. In fact, Raufman *et al.* describes incubating the acinar suspension with exendin-4 or GLP-1(7-36) for only 30 minutes.

See page 21433, col. 1, 5th full paragraph. Therefore, claims 2, 13, 25 and 29 cannot be rejected on the basis of express anticipation.

With regard to the Office Action's rejection of claims 2, 13, 25 and 29 on the basis of inherency, the Office has the burden to show that Raufman *et al.* inherently describes an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor, for example GLP-1(7-36) and/or exendin-4.

Raufman *et al.* does not mention differentiating non-insulin-producing cells into insulin-producing cells. In fact, the reference studied the effect of GLP-1(7-36) on exendin receptors and subsequent changes in cAMP and amylase secretion in the acinar cells of guinea pigs. Nothing is disclosed in the reference to demonstrate that differentiating non-insulin-producing cells into insulin-producing cells was part of the problem to be solved.

Further, the Office is incorrect if it assumes that incubating acinar cells with GLP-1(7-36) *in vitro* for only up to 30 minutes will necessarily differentiate some of those cells into insulin-producing cells. As noted above, the instant application teaches an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof. Applicants disclose that it took at least twenty-four hours of contact with the growth factor for non-insulin-producing cells to differentiate into

insulin-producing cells. See Example 3 in the instant application. Thus, in the method of Raufman *et al.*, in which contact between acinar (non-insulin-producing) cells and GLP-1(7-36) or exendin-4 lasted for only about 30 minutes, a person of skill in the art would not expect to find differentiation of those cells into insulin-producing cells. Thus, the Office has the burden to show that the missing matter in this reference, an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof, is necessarily present. *Hansgirg*, 102 F.2d 212.

It is error for the Office to reject claims 2, 13, 25 and 29 because it is possible or even probable that some of the insulin-producing cells claimed in the instant application may have been present in Raufman *et al.* The Examiner has failed to show with certainty that the missing matter (the cells) is present, and thus, there can be no anticipation of these claims based on inherency. Therefore, applicants respectfully request that this rejection be withdrawn and that claims 2, 13, 25 and 29 be allowed.

C. Claims 1, 3-10, 23, 26 and 31 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 95/31214, issued to Dupre. The Office Action states that Dupre discloses a method of treating Type 1 diabetes with GLP-1 analog (GLIP) by ways such as i.v. infusion and indicates that the use of GLIP in treating Type 1 diabetes provides improved glycemic control. The Office Action goes on to allege that a population of insulin-producing

cells would inherently exist in the treated patients because the prior art consists of the same steps described in the present claims.

Claims 1, 23 and 31 are amended herein by adding the phrase "for at least twenty-four hours." Claims 3-10 and 26 depend upon these amended claims. WO 95/31214 does not expressly disclose each and every element of these amended claims. Specifically, the patent does not teach that the growth factor contacts non-insulin-producing cells for at least twenty-four hours. In WO 95/31214, the growth factor was administered to subjects for no greater than 2 hours. Therefore, amended claims 1, 23 and 31 cannot be rejected on the basis of express anticipation.

With regard to the Office Action's rejection of claims 1, 3-10, 23, 26 and 31 on the basis of inherency, the Office has the burden to show that WO 95/31214 inherently describes an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor selected from the group consisting of GLP-1, growth factors having amino acid sequences substantially homologous to GLP-1, and fragments thereof.

WO 95/31214 teaches the use of GLIP in combination with insulin for treating Type 1 diabetes. The subjects diagnosed with Type 1 diabetes were in remission and were characterized "by substantial remaining endogenous insulin secretion." See page 5, lines 4-7. The patent also teaches that GLIP alone, when administered in a two hour infusion, can be used to treat Type 1 diabetic patients who have some endogenous insulin secretion because GLIP stimulates insulin

secretion from pancreatic beta cells and helps to control the rise in blood sugar after a meal because it delays gastric emptying. Thus, this patent discloses that GLIP can be used to treat diabetics who can still secrete insulin based on two different mechanisms, i.e., by stimulating insulin secretion from insulin-producing cells and/or by delaying gastric emptying.

WO 95/31214 does not teach the use of GLIP for treating diabetic patients who no longer have endogenous insulin secretion. Moreover, the patent does not mention differentiating non-insulin-producing cells into insulin-producing cells. Nothing is disclosed in WO 95/31214 to demonstrate that differentiating non-insulin-producing cells into insulin-producing cells was part of the problem to be solved.

Further, it is erroneous to assume that methods of stimulating insulin release in a mammal as taught in WO 95/31214 necessarily differentiates non-insulin-producing cells into insulin-producing cells. The patent teaches administering GLIP in a two hour infusion, alone or in combination with insulin, to stimulate endogenous secretion of insulin in patients with insulin-secreting cells. In fact, the patent discloses that "[i]t may be that the improved glycaemic control seen with GLIP administration in Type 1 diabetics is due to delay of the post-meal rise in blood glucose through the interval required for the establishment of the effect of insulin." See page 6, lines 14-18.

In contrast, the instant application teaches an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor selected from the group consisting of GLP-1 and/or

exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof. Applicants disclose that it took at least twenty-four hours for non-insulin-producing cells to differentiate into insulin-producing cells. See in the specification page 41, lines 19-22. Thus, in the method of WO 95/31214, in which contact between non-insulin-producing cells and GLIP lasted for only about two hours, a person of skill would not expect to find differentiation of those cells into insulin-producing cells. Thus, the Office has the burden to show that the missing matter in this reference, an isolated population of insulin-producing cells made by a process comprising contacting, for at least twenty-four hours, non-insulin producing cells with a growth factor selected from the group consisting of GLP-1 and/or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1 and/or exendin-4, and fragments thereof, is necessarily present. *Hansgirg*, 102 F.2d 212.

Even if the Examiner thinks it is possible or even probable that some of the insulin-producing cells claimed in the instant application may have been present in WO 95/31214, the legal standard is not satisfied. The Examiner has failed to show with certainty that the missing matter (the cells) is present, and, thus, there can be no anticipation of these claims based on inherency. Therefore, applicants respectfully request that this rejection be withdrawn and that amended claims 1, 23 and 31 and dependent claims 3-10, and 26 be allowed.

D. Claim 31 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Mashima *et al.* (*Endocrinology*, 1996, 137(9): 3969-76. The Office Action states that this reference discloses a method of enriching a population of cells for insulin-producing cells by treating cells with a growth factor such as hepatocyte growth factor (HGF) and demonstrates that

pancreatic AR42J cells derived from acinar cells, when treated with HGF, were converted into insulin-producing cells.

Claim 31 is amended herein to recite "[a] method of enriching a population of cells for insulin-producing cells, comprising contacting, for at least twenty-four hours, the population of cells with GLP-1 or exendin-4, growth factors having amino acid sequences substantially homologous to GLP-1or Exendin-4, or fragments thereof, that differentiate non-insulin-producing cells into insulin-producing cells." Applicants believe that the amendment overcomes this rejection and respectfully request that this rejection be withdrawn and that amended claim 31 be allowed.

35 U.S.C. § 103(a)

A. Claims 11, 22, 24 and 28 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Eng, U.S. Patent No. 5,424,286 (the '286 patent) as applied to claims 1, 3-10, 12, 14-21, 23, 26, 27, 30, 31, and 36-38.

Claims 11, 22, 24 and 28 are canceled herein, thereby rendering this rejection moot as applied to these claims. Applicants, therefore, respectfully request that this rejection be withdrawn.

Claims 1, 12, 23, 27 and 31 are amended herein by the addition of the phrase "for at least twenty-four hours." Further, claim 36 is amended to recite "[a] method of inducing insulin secretion in a subject, comprising administering to the subject a growth factor selected from the

group consisting of Exendin-4, growth factors having amino acid sequences substantially homologous to Exendin-4, and fragments thereof, wherein the Exendin-4 contacts non-insulin-producing cells for at least twenty-four hours, and wherein the non-insulin-producing cells are differentiated into insulin-producing cells."

The Office has the burden of establishing a *prima facie* case of obviousness. Specifically, the Office has the burden to show 1) that the prior art would have suggested to those of ordinary skill in the art that they should make the claimed method and 2) that the prior art would have revealed that in so carrying out the method, those of ordinary skill would have a reasonable expectation of success. See *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

The '286 patent does not suggest to a person of skill in the art that the growth factor should be in contact with the target cells for at least twenty-four hours. Moreover, the patent does not suggest or teach with a reasonable expectation of success that administering a growth factor to a subject will differentiate non-insulin-producing cells into insulin-producing cells. In fact, the '286 patent teaches away from the instant application because the patent states, "FIG. 4 shows a dose response curve to exendin-4 indicating that exendin-4 acts directly on beta cells to stimulate insulin secretion." (Emphasis added.) See col. 8, lines 13-26. Thus, this patent would not motivate a person of skill to contact non-insulin-producing cells with a growth factor for at least twenty-four hours to stimulate insulin secretion. Therefore, applicants believe that the Examiner has failed to make a *prima facie* case for obviousness and respectfully request that

amended claims 1, 12, 23, 27, 31 and 36 and dependent claims 3-10, 14-21, 26, 30 and 37-38 be allowed.

B. Claims 34 and 35 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Dupre (WO 95/31214), as applied to claims 1, 3-10, 23 26 and 31. The Office Action states that the reference does not teach continuous infusion with said compound for at least twenty-four hours as claimed; however, given the current state of the art, determination of an appropriate regimen of treatment with a drug is allegedly within the purview of a person of ordinary skill in the art.

Claim 34 is amended herein to recite "[a] method of inducing insulin secretion in a subject lacking insulin-producing cells, comprising administering to the subject a growth factor selected from the group consisting of GLP-1, growth factors having amino acid sequences substantially homologous to GLP-1, and fragments thereof by continuous infusion for at least twenty-four hours."

WO 95/31214 does not teach or suggest a method of inducing insulin secretion in a subject lacking insulin-producing cells. As noted above, the patent teaches the use of GLIP in combination with exogenous insulin for treating Type 1 diabetes. The subjects studied in this patent were members of a small, unusual subclass of Type 1 diabetics who were in remission and were characterized as having "substantial remaining endogenous insulin secretion." See page 5, lines 4-7. The patent teaches that GLIP alone, when administered in a two hour infusion, can be used to treat Type 1 diabetic patients in remission because GLIP stimulates insulin secretion

from remaining pancreatic beta cells and helps to control the rise in blood sugar after a meal because it delays gastric emptying.

However, WO 95/31214 does not teach the use of GLIP for treating patients diagnosed with Type 1 diabetes who do not have any endogenous insulin secretion. In fact, the patent teaches that "[i]t may be that the improved glycaemic control seen with GLIP administration in Type 1 diabetics is due to delay of the post-meal rise in blood glucose through the interval required for the establishment of the effect of insulin." See page 6, lines 14-18.

Moreover, a person of skill who practices the method of WO 95/31214 would not have a reasonable expectation of inducing insulin secretion in a subject lacking insulin-producing cells because the reference does not teach that a two hour infusion of GLIP causes insulin secretion in a subject who has no naturally occurring insulin-producing cells. Further, the reference does not suggest or teach that GLIP can differentiate non-insulin-producing cells into insulin-producing cells after at least a twenty-four hour exposure.

Because WO 95/31214 does not suggest to those of ordinary skill the claimed method, and because WO 95/31214 does not teach a reasonable expectation of success for the claimed method, the Office has failed to make its *prima facie* case for obviousness. Therefore, applicants respectfully request that this rejection be withdrawn and that amended claim 34 and dependent claim 35 be allowed.

ATTORNEY DOCKET NO. 14014.0346U1
PATENT

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $1,410.00 ($1,300.00 (fee for a Petition to Accept an Unintentionally Delayed Claim for Priority, pursuant to 37 C.F.R. § 1.17(t)), and $110.00 (fee for one month extension of time)) is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Tina W. McKeon
Registration No. 43,791

NEEDLE & ROSENBERG, P.C.
Customer No. 36339
(404) 688-0770
(404) 688-9880 (fax)

CERTIFICATE OF FACSIMILE

I hereby certify that this correspondence is being sent via facsimile to: Examiner D. Jiang at (703) 308-0294, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Tina W. McKeon

May 6, 2003
Date